REMARKS/ARGUMENTS

The Invention

The invention is directed to a method of inhibiting metastasis of a tumor cell in a mammal. The tumor cell expresses CXC Chemokine Receptor-4 (CXCR4) and the method comprises administering to the mammal a polypeptide of SEQ ID NO: 1 or a CXCR4 antagonist that is not an antibody that binds CXCR4 in an amount sufficient to inhibit metastasis of the tumor cell. The invention also is directed to a method of inhibiting growth of a tumor cell comprising administering to the tumor cell a polypeptide of SEQ ID NO: 1.

The Pending Claims

Claims 1-11 and 36-39 are currently pending. Claims 1-11 are directed to the method of inhibiting metastasis of a tumor cell, and claims 36-39 are directed to the method of inhibiting growth of a tumor cell.

The Office Action

Claims 1-11 and 36-39 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Koshiba et al., *Clinical Cancer Research, 6*, 3530-35 (2000) ("Koshiba") alone or in combination with WO 99/50461 (Murphy et al.) ("the Murphy PCT application") and WO 99/47158 (Clark-Lewis) ("the Clark-Lewis PCT application"). Reconsideration of these rejections is respectfully requested.

Discussion of Rejections Under 35 U.S.C. § 103

Claims 1-11 and 36-39 remain rejected under Section 103 as allegedly obvious over Koshiba alone or in combination with the Murphy PCT application and the Clark-Lewis PCT application. For the reasons set forth below, the Office has not presented sufficient evidence to establish *prima facie* obviousness under Section 103.

The Office bears the burden of proof when rejecting a claim as obvious in view of the prior art. *In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In order to meet that burden, the Office must show both that the prior art would have suggested the claimed invention to one of ordinary skill in the art, *and that one of ordinary skill in the art would reasonably expect that the method would be successful.* Furthermore, to protect against the

improper use of hindsight, both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

The Office acknowledges the express statement in Koshiba that the *in vivo* role of the T22 polypeptide with respect to metastasis is *unknown*. Nevertheless, the Office concludes that the use of T22 to inhibit metastasis *in vivo* would have been obvious to one of ordinary skill in the art because (a) Koshiba considers the mechanisms involved and hypothesizes that CXCR4 receptor-ligand interactions may be involved in tumor cell migration, and (b) Koshiba states that *in vivo* tests are warranted. Specifically, the Office states: "This is not a statement that it is obvious to try but that one should go out and perform these tests on *in vivo* models" (see Office Action at pp. 3-4). The Office relies upon the Murphy PCT and the Clark-Lewis PCT as evidence of a reasonable expectation that T22 could be successfully used *in vivo*.

Koshiba's statements that CXCR4 interactions *may* be involved in metastasis, or that *in vivo* tests are warranted do not establish a reasonable expectation of success that T22 can be used *in vivo*. Koshiba acknowledges that such statements are hypotheses contingent on factors that could affect T22 *in vivo*: "The mode of action of chemokines depends heavily on the local environment ... The secreted protein may be localized by binding to the extracellular matrix. In this situation, *in vitro* migration assays may not predict *in vivo* function" (Koshiba at p. 3535). Also, contrary to the Office's interpretation, a statement to "go out and perform tests *in vivo*" is, explicitly and unequivocally, an invitation to experiment, which can only support an "obvious to try" rationale.

Furthermore, the Office cannot properly ignore Koshiba's express statement that the *in vivo* role of T22 is *unknown*. A reference must be considered in its entirety, including disclosures that teach away from a claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). When considered in its entirety, Koshiba's clear and definite statement that the *in vivo* role of T22 is *unknown*, outweighs Koshiba's equivocal statements that T22 *might* be involved in metastasis, or that further *testing* is warranted. This is especially true when considering that Koshiba provides explicit reasons why T22 might *not* work *in vivo* (see above).

The Federal Circuit held in *In re Gangadharam* that the PTO failed to present a *prima facie* case of obviousness based on very similar facts. *In re Gangadharam,* 13 U.S.P.Q.2d

1568 (Fed. Cir. 1989) (unpublished opinion). In *Gangadharam*, the court considered the obviousness rejection of claims directed to an *in vivo* method of using a compound based on a reference disclosing encouraging *in vitro* tests of a compound. *Id.* at 1568. The court held that a statement in the prior art that positive *in vitro* results favor *in vivo* use does not meet the statutory standard for obviousness because such statements, even when coupled with favorable *in vitro* testing, do not provide a reasonable expectation of success. *Id.* at 1570 (citing *In re Carroll*, 202 USPQ 571 (CCPA 1979)). The court stressed that a reference must be considered for all that it teaches, and the enumeration of variables necessary for success *in vivo* could indicate to one of ordinary skill that there is not a reasonable expectation of success *in vivo*. *Id.* at 1569 (citing *W.L. Gore & Assoc. v. Garlock, Inc.*, 220 USPQ 303, 311 (Fed. Cir. 1983)).

As in *Gangadharam*, Koshiba merely provides *in vitro* testing coupled with equivocal statements that CXCR4 *may* play a role in metastasis, and that *in vivo* testing is required. These statements are further qualified by the author's assertions that the *in vitro* tests may not be probative of *in vivo* efficacy for specific reasons, and that the *in vivo* role of T22 is unknown. When considered in its entirety, Koshiba does not provide a reasonable expectation of success that T22 could be used *in vivo*.

Furthermore, it was well known in the art at the time the subject application was filed that compounds which show activity against a particular disease *in vitro* often do not exhibit efficacy *in vivo*. For example, Brook, *Rev. Infect. Dis.*, *13*(6): 1181-3 (1991) (copy of abstract enclosed herewith) discloses several antimicrobial agents that exhibit *in vitro* activity against specific bacterial strains; however, only a subset of these antimicrobial agents successfully treated bacterial infections *in vivo*. The authors conclude that "[t]hese data illustrate the complexity and difficulties encountered when *in vitro* activity is correlated with *in vivo* efficacy" (Brook at Abstract).

Neither the Murphy PCT application nor the Clark-Lewis PCT application provides a reasonable expectation that T22 could successfully be used *in vivo*. The Murphy PCT and Clark-Lewis PCT do not disclose the use of T22. Rather, these references disclose the use of CXCR4 antagonists that are quite dissimilar from T22. Moreover, other than stating generally that T22 is a CXCR4 antagonist, the Office provides no evidence or reasoning to suggest how the disclosures of the Murphy PCT or Clark-Lewis PCT provide a reasonable expectation that T22, a completely different molecule from that disclosed in the cited

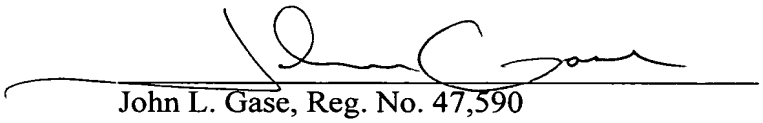
references, could be used *in vivo*. The Office does not, for instance, allege any similarity in structure between T22 and the molecules cited in the PCT references, nor provide any evidence that all members of the broad class of CXCR4 antagonist would be expected to behave in the same way *in vivo*. It is the Office's burden to provide such evidence. The Applicant need not rebut the Office's allegations until after it has established a *prima facie* case.

For the foregoing reasons, the Section 103 rejection is improper and should be withdrawn.

Conclusion

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: January 17, 2006

1: Rev Infect Dis. 1991 Nov-Dec;13(6):1170-80.

Comment in:
Rev Infect Dis. 1991 Nov-Dec;13(6):1181-3.

In vitro susceptibility vs. in vivo efficacy of various antimicrobial agents against the Bacteroides fragilis group.

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In vitro susceptibility testing is only one step in the evaluation of the potential efficacy of antimicrobial agents against the Bacteroides fragilis group. An assessment of in vivo efficacy, with a consideration of the factors that can best be studied in an infected host, is also an integral part of this process. Abscess models in rodents have been used to correlate in vitro activity with in vivo efficacy against this group of microorganisms. For metronidazole, clindamycin, moxalactam, and cefoxitin, the correlation was strong; for chloramphenicol and carbenicillin, it was not. In vivo studies of mixed infection with the B. fragilis group and Escherichia coli showed that cefoxitin and imipenem were effective; in contrast, cefotetan was not effective against resistant strains. Only strains susceptible to ceftizoxime in the agar dilution test were also affected by this drug in vivo. The so-called inoculum effect noted with ceftizoxime may explain this finding. In vivo elimination of encapsulated organisms of the B. fragilis group was found to be more difficult than elimination of unencapsulated isolates. The beta-lactamase produced by Bacteroides species can protect the enzyme-producing organism as well as its partners in mixed infections from the effects of beta-lactam antibiotics. These data illustrate the complexity and difficulties encountered when in vitro activity is correlated with in vivo efficacy.

Publication Types:
Review

PMID: 1775850 [PubMed - indexed for MEDLINE]